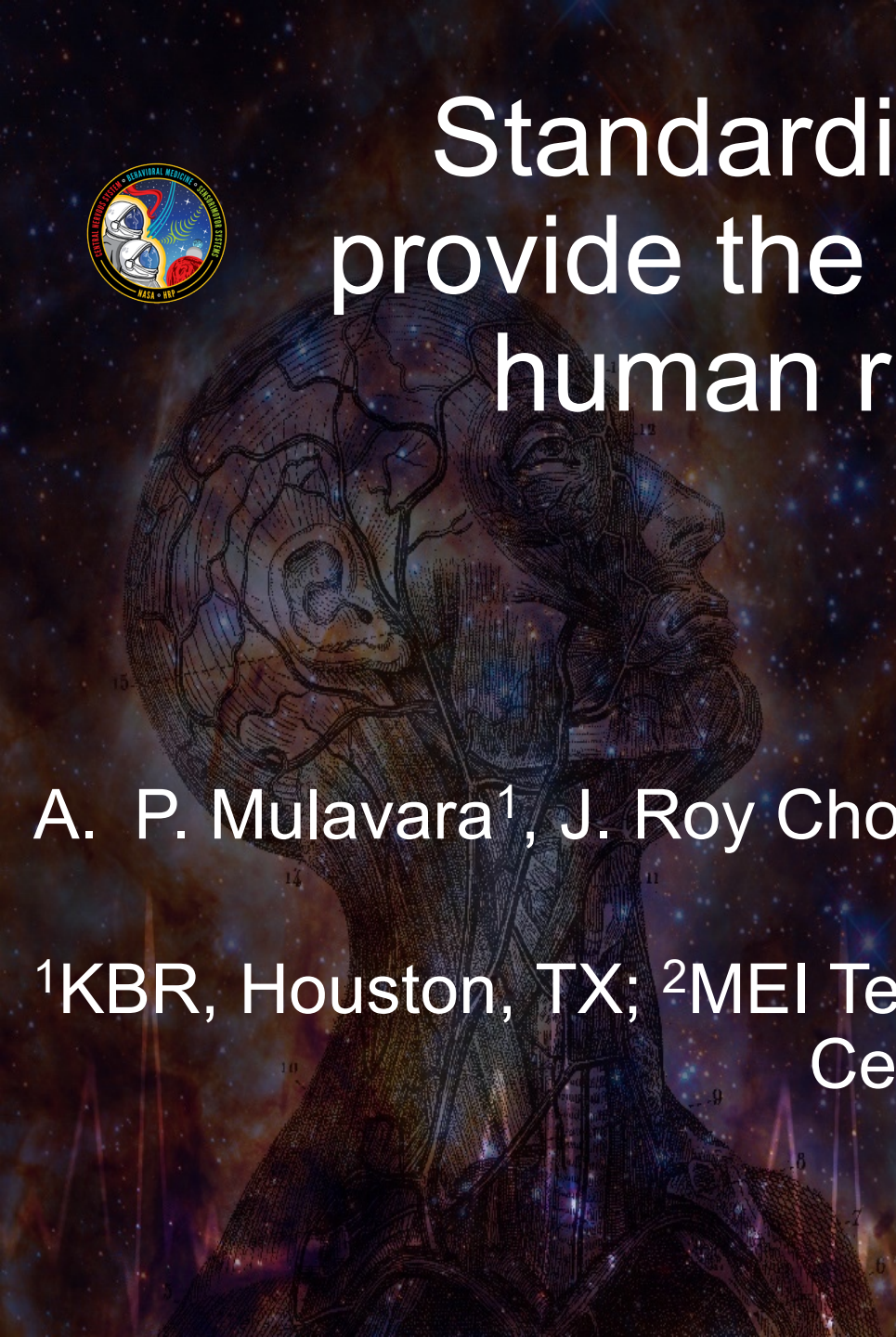
Standardizing rodent models to provide the most valid translation to human risks from spaceflight



HRP IWS 2020

January 27, 2020

A. P. Mulavara[1], J. Roy Choudhury[2], A. Hanson[3], K. George[1], A. Whitmire[3], T.J. Williams

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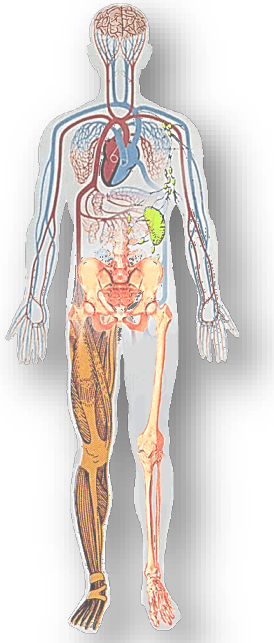
Introduction

Introduction to CBS

Balance Disorders
Fluid Shifts
Cardiovascular Deconditioning
Muscle Atrophy
Bone Loss

Acute In-flight effec
Long-term cance
risk
CNS-Cognitive



Integrated Research Plan:

- **C**NS acute effects of radiation
- **B**ehavioral Medicine
- **S**ensorimotor

Behavioral aspect of isolation
Sensory deprivation
Sleep disorders (circadian dysregulation)

CBS Integrated Research Plan

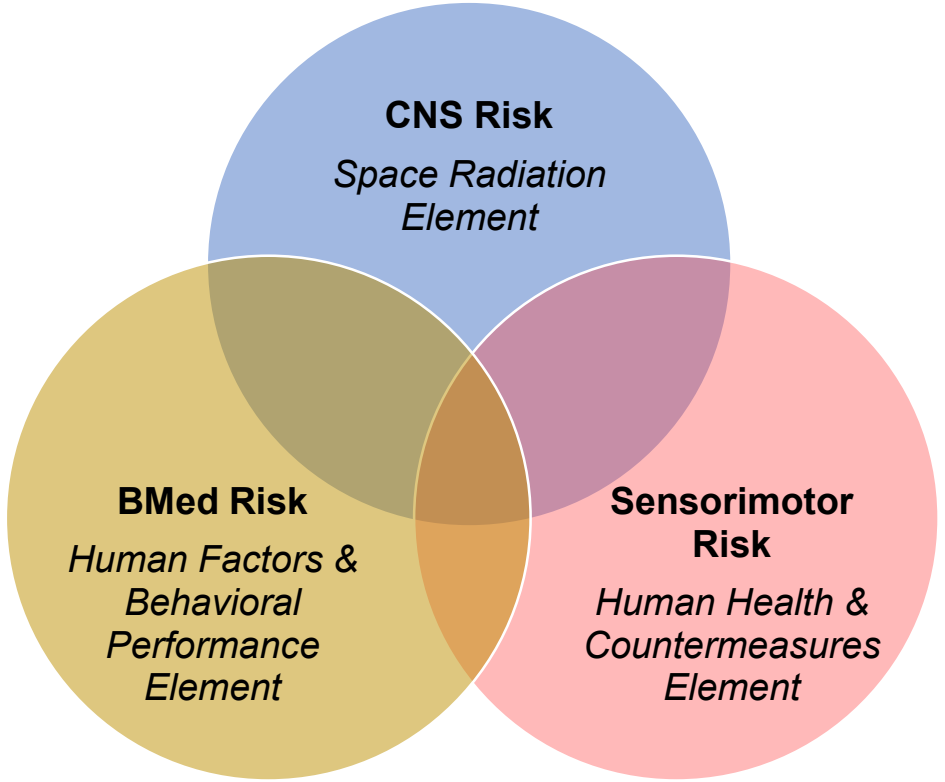
Designed to accelerate discovery (the identification), and mitigation (monitoring and countermeasures development) of the potentially synergistic effects of the 3 spaceflight hazards on operationally relevant tasks, to ensure crew safety and mission success.

*Spaceflight hazards **GUIDE** the Risk Management process, help to **PRIORITIZE** research tasks, and **FOCUS** our operational implementation of monitoring tools and countermeasures.*

CBS Integrated Research Plan

Research Strategy

Designed to accelerate discovery (the identification), and mitigation (monitoring and countermeasures development) of the potentially synergistic effects of the 3 spaceflight hazards, to ensure crew safety and mission success.



Research Strategy: Individual Risks

HRP Element	CBS Associated Risk
Space Radiation (SR)	Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation (CNS)
Human Factors and Behavioral Performance (HFBP)	Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders (BMed)
Human Health Countermeasures (HHC)	Risk of Impaired Control of Spacecraft/Associated Systems and Decreased Mobility Due to Vestibular/Sensorimotor Alterations Associated with Spaceflight (SM)

CBS Integrated Research Plan: Individual HRP Risk Areas with associated Gaps

Risks →

Gaps ↑ ↓

Effects of Acute (Inflight) Space Radiation Exposure	Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders	Vestibular/Sensorimotor Alterations Associated with Spaceflight
CNS - 1: Are there significant adverse changes in CNS performance in the context and time scale of spaceflight operations? If so, how is significance defined, and which neuropsychological domains are affected? Is there a significant probability that space radiation exposure would result in adverse changes? What are the pathways and mechanisms of change?	**BMed1:** We need to identify and validate countermeasures that promote individual behavioral health and performance during exploration class missions.	**SM2.1:** Determine the changes in sensorimotor function over the course of a mission and during recovery after landing.
CNS - 2: Does space radiation exposure elicit key events in adverse outcome pathways associated with neurological diseases? What are the key events or hallmarks, their time sequence and their associated biomarkers (in-flight or post-flight)?	**BMed2:** We need to identify and validate measures to monitor behavioral health and performance during exploration class missions to determine acceptable thresholds for these measures.	**SM6.1:** Determine if sensorimotor dysfunction during and after long-duration spaceflight affects ability to control spacecraft and associated systems.
CNS - 3: How does individual susceptibility including hereditary pre-disposition (e.g. Alzheimer's, Parkinson's, apoE allele) and prior CNS injury (e.g. concussion, chronic inflammation or other) alter significant CNS risks? Does individual susceptibility modify possible threshold doses for these risks in a significant way?	**BMed3:** We need to identify and quantify the key threats to and promoters of mission relevant behavioral health and performance during autonomous, long duration and/or long distance exploration missions.	**SM7.1:** Determine if there are decrements in performance on functional tasks after long-duration spaceflight. Determine how changes in physiological function, exercise activity, and/or clinical data account for these decrements.
CNS - 4: What are the most effective medical or dietary countermeasures to mitigate CNS risks? By what mechanisms are the countermeasures likely to work?	**BMed5:** We need to identify and validate measures that can be used for the selection of individuals that are highly resilient to the key behavioral health and performance threats during autonomous, long duration and/or long distance exploration missions.	**SM24:** Determine if the individual capacity to produce adaptive change (rate and extent) in sensorimotor function to transitions in gravitational environments can be predicted with preflight tests of sensorimotor adaptability.
CNS - 5: How can new knowledge and data from molecular, cellular, tissue and animal models of acute CNS adverse changes or clinical human data, including altered motor and cognitive function and behavioral changes be used to estimate acute CNS risks to astronauts from GCR and SPE?	**BMed6:** We need to identify and validate effective treatments for adverse behavioral conditions and psychiatric disorders during exploration class missions.	**SM26:** Determine if exposure to long-duration spaceflight leads to neural structural alterations and if this remodeling impacts cognitive and functional performance.
CNS - 8: Are there significant CNS risks from combined space radiation and other physiological or space flight factors, e.g., psychological (isolation and confinement), altered gravity (micro-gravity), stress, sleep deficiency, altered circadian rhythms, hypercapnea, altered immune, endocrine and metabolic function, or other?		**SM28:** Develop a sensorimotor countermeasure system integrated with current exercise modalities to mitigate performance decrements during and after spaceflight.

CBS Integrated Research Plan
Research Emphases (RE) to Inform the Combined Risk

Research Strategy

RE 1: Standardized models to provide most valid translation from rodent to humans for ground testing.

RE 2: Operational performance measures that will best indicate CBS performance decrements in ground and flight.

RE 3: Crew Health & Performance Standards that adequately protect crew during exploration class missions.

RE 4: Systematically assessed effects of radiation type & dose-rates on operationally relevant CNS/BMed/SM brain performance pathways & mechanisms.

RE 5: Validated method for predicting CBS performance decrements due to mission-expected radiation exposures.

RE 6: Countermeasures that maintain crew performance standards during exploration class missions.

CBS Integrated Research Plan
Overall Research Strategy

Research Strategy

Review Evidence Base/ Data Mining:
What has our research to date demonstrated? Spaceflight Hazards: Space Radiation/Isolation & Confinement/Altered Gravity impacts on CNS/Bmed/SM

Shape Policy

Translational Models to Accelerate Knowledge Base of CBS Combinatorial Effect
Leverage modeling & research outcomes using biomarkers and determine performance/exposure relationships via Brain Performance Pathway: establish first POLs & PELs

Crew Health Standards POLs & PELs
Validate / Implement POLs/PELs & CMs

Computational Modeling
To heuristically determine biological effects that lead to Brain Performance Pathway Changes

Countermeasures, Monitoring Tools
Determine individual sensitivities, biomarkers and countermeasures to mitigate risks

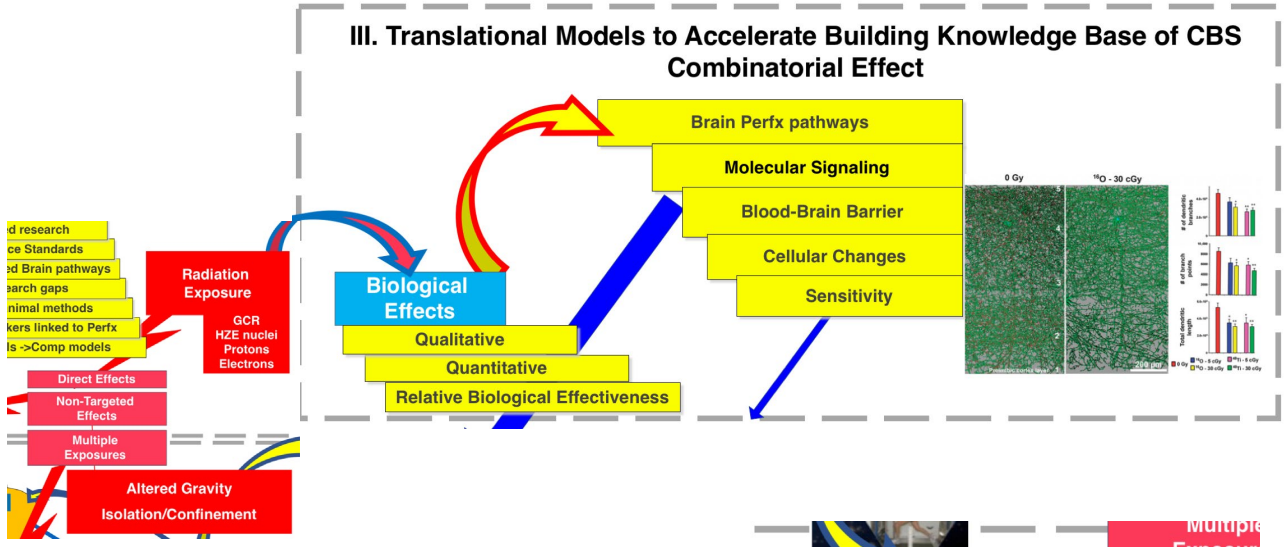
Bridge w/animal models & translation

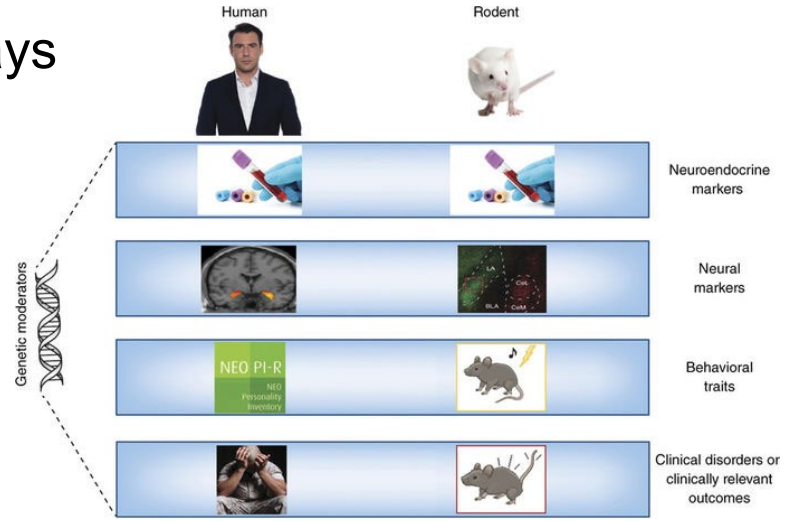
Translational Models

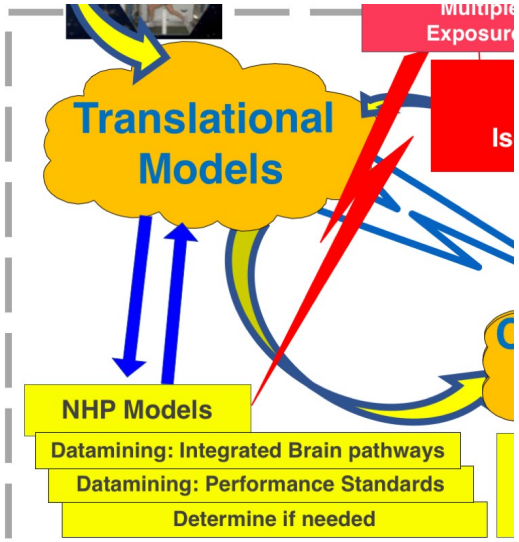
Determine Biological Effects that Lead to Brain Changes

Research emphases: research areas and techniques

- Using animal models (facilities, strains, approaches) with translation & reverse translation, research domain criteria
  - Identify biomarker linkage
  - Identify brain structure & functional changes
  - Identify performance pathways
- Non-human primates



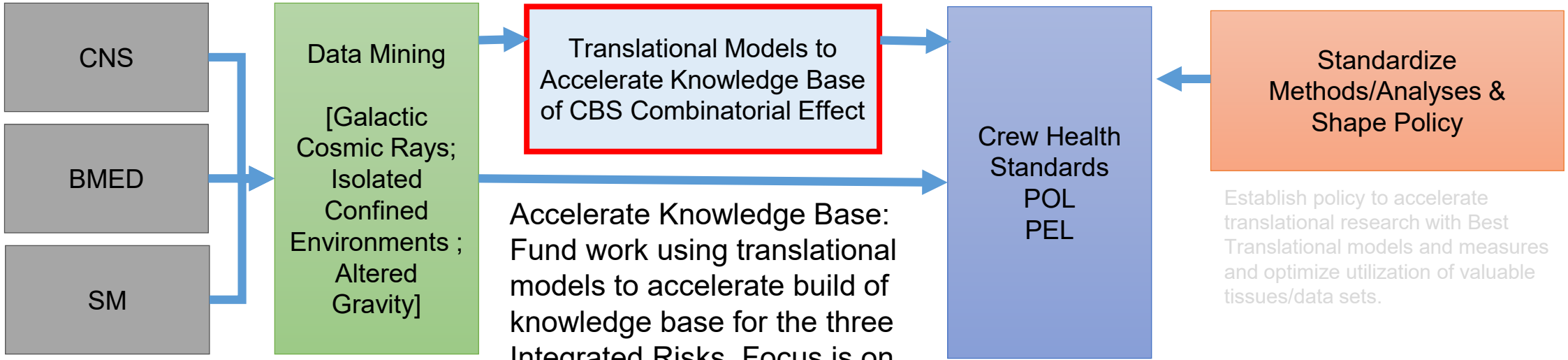




Translational Models

- RE #2 - Operational performance measures that will best indicate CBS performance decrements in ground and flight.
- RE #4 - Systematically assess effects of radiation type & dose-rates on operationally-relevant CNS/Bmed/SM brain performance pathways & mechanisms.

Research emphases: research areas and techniques



Review evidence base from 3 Risks to determine state of collective knowledge.

Perform Data Mining on identified integrated knowledge gaps, to guide forward work.

Emphasis on operationally relevant performance outcomes, brain pathways, and biomarkers.

Update respective CNS, BMED, and SM Standards as required and establish new CBS POLs/PELs by 2026.

Establish policy to accelerate translational research with Best Translational models and measures and optimize utilization of valuable tissues/data sets.

Standardization of Methods and Analysis

Review of Evidence Base / Data Mining & Shape Policy

Research emphases: research areas and techniques

Goals of 'Review Evidence Base / Data Mining & Shape Policy' include:

- Identify standard tests in humans and equivalent translational models.
- Identify "biomarkers" via brain performance pathways affecting operationally relevant performance.
- Evaluate availability/mode of action/needs for countermeasures.
- Inform via technical interchange meeting / workshops – Intra/Extra mural experts.

Concept of Translation
e.g. Postural control brain network

Research emphases: research areas and techniques

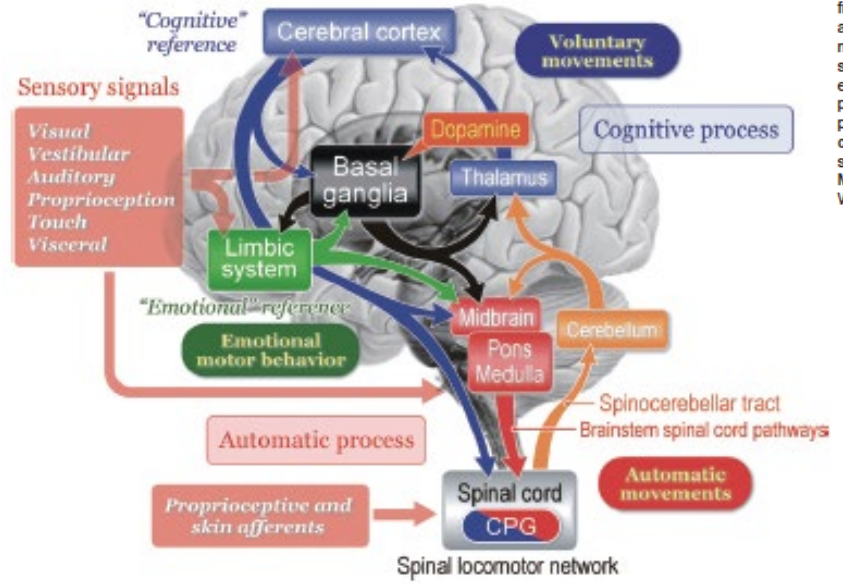
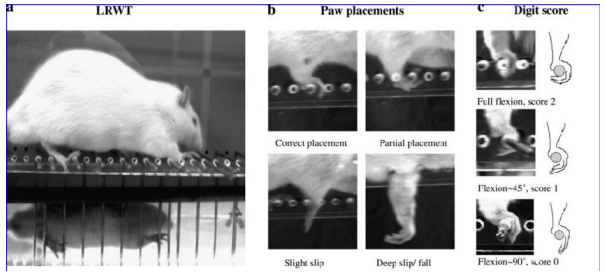
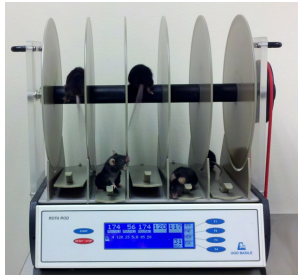


Figure 1. Basic signal flow involved in postural control. Multisensory signals from the visual, vestibular, auditory, somatosensory (proprioceptive), and visceral receptors act on various sites in the central nervous system. These signals may provide cognitive and emotional references to the cerebral cortex and limbic system, respectively, so that the subject may elicit either voluntary movements or emotional motor behavior depending on the context. In each case, automatic process of postural control, such regulation of postural muscle tone and basic postural reflexes, by the brainstem and spinal cord is required. On the other hand, cognitive postural control is particularly important when the subject learns motor skills and behaves in unfamiliar circumstance. See text for detail explanation. Modified from Takakusaki. Mov Disord 2013;28:1483-1491, with permission of Wiley.[5]



Ladder Rung Walk Test

Journal of neurotrauma 26(1):17-29 · February 2009



Mouse Rotarod Test

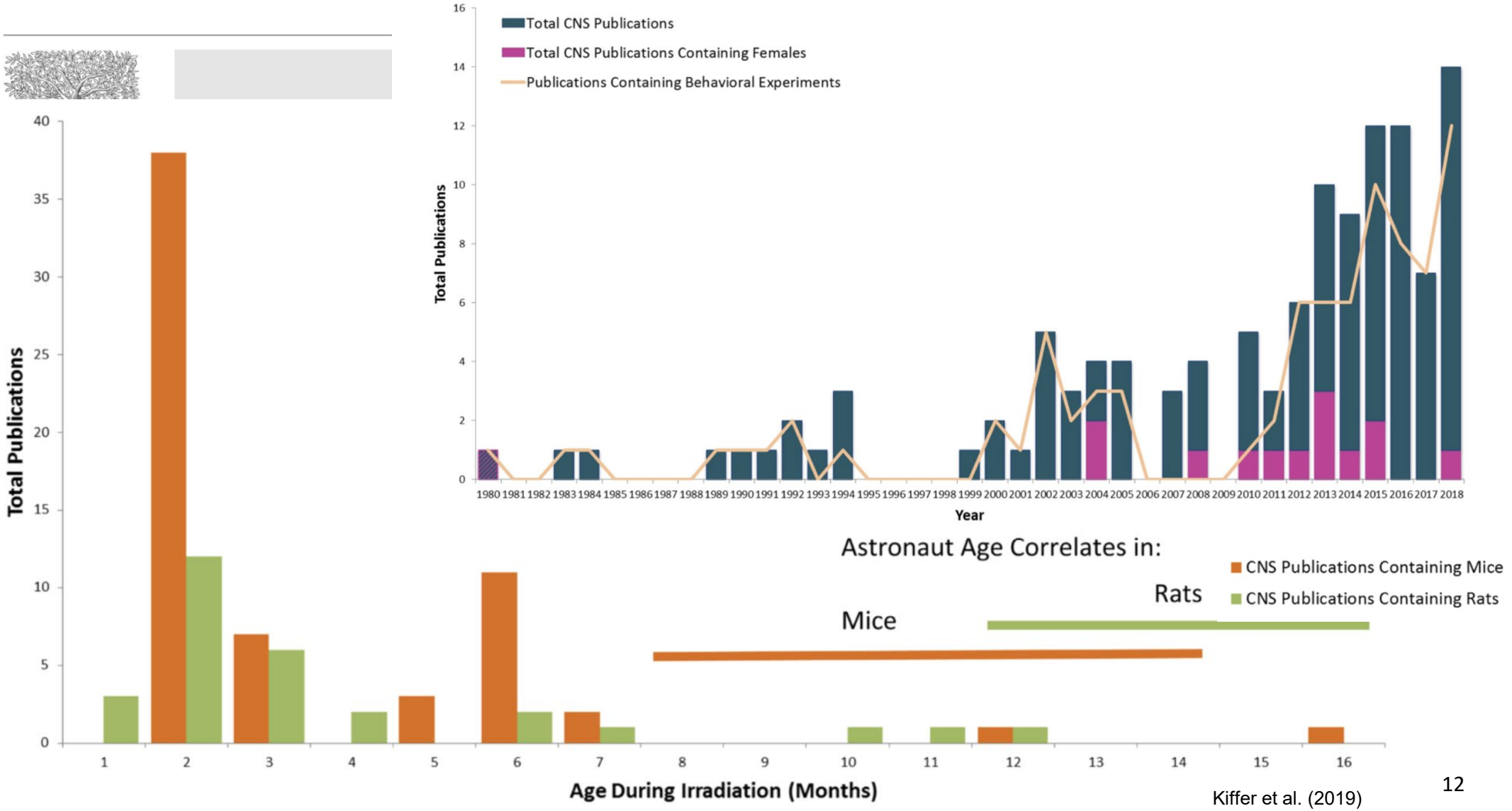
https://en.wikipedia.org/wiki/Rotarod_performance_test#/media/File:Mouse_RotaRod.png

Tandem Walk Test

Bloomberg JJ (PI) FTT test

Evidence of the Need to Standardize Approaches

Research emphases: research areas and techniques



Kiffer et al. (2019)

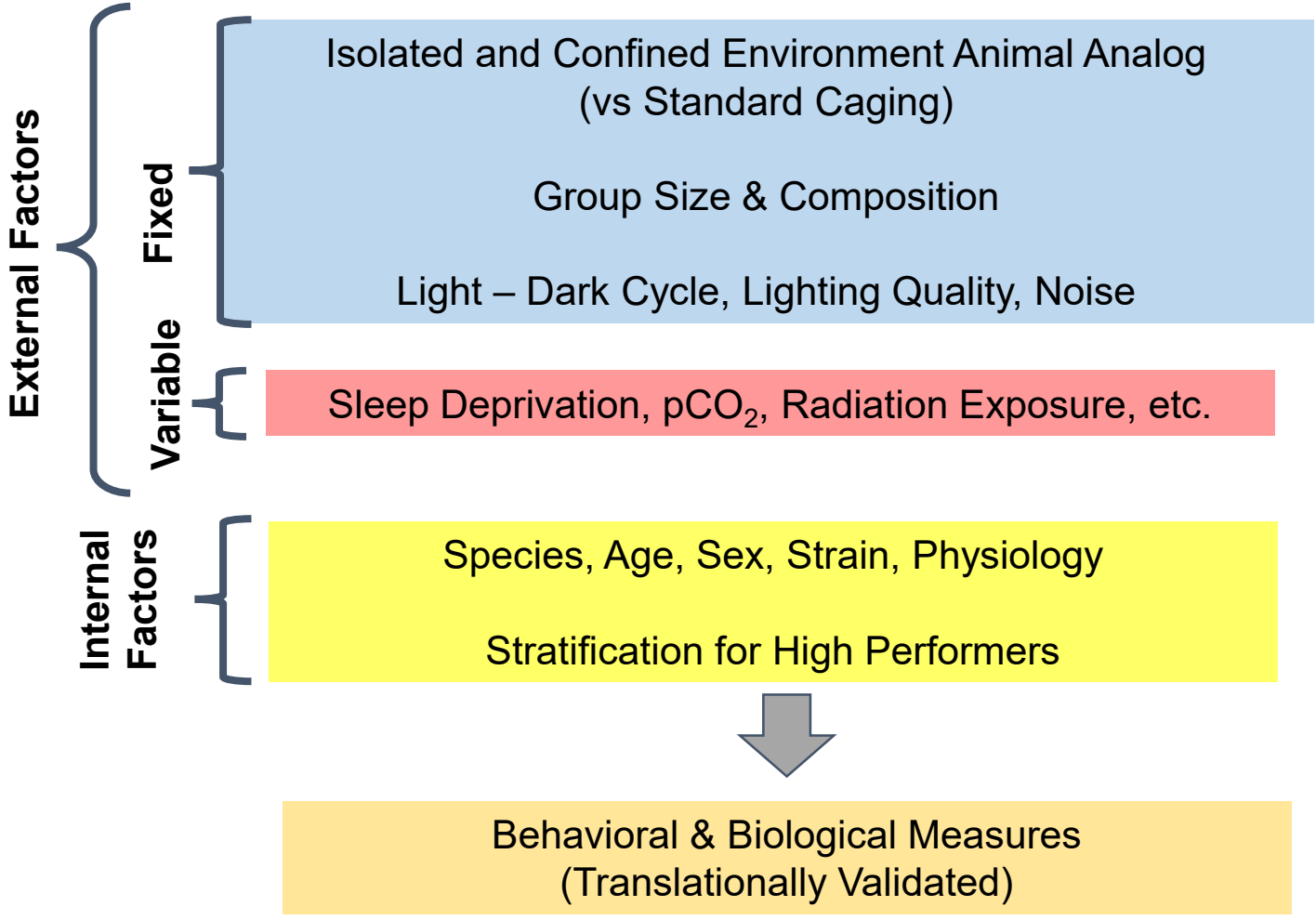
Standardization of Methods and Analysis

Review of Evidence Base / Data Mining & Shape Policy

Research emphases: research areas and techniques

Technical Interchange Meetings

What Standard Experimental Conditions are Needed?

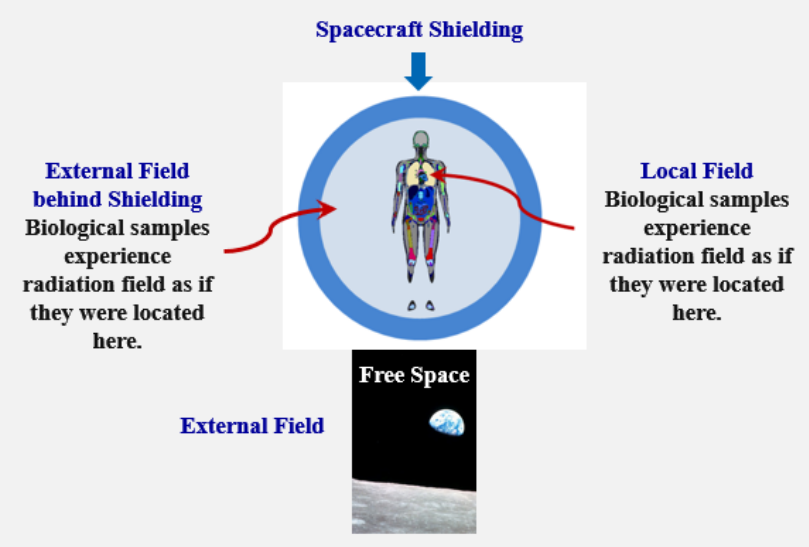


Nelson G (2017, TM I)

NASA Space Radiation Laboratory GCR Simulation

Research emphases: research areas and techniques

Defined and delivered GCR reference environment radiation field compatible with NSRL operational and delivery parameters including animal care, cell requirements and logistics.



The radiation field found within the female deep tissue site (BFO) behind 20g/cm^{2}of aluminum during solar minimum conditions is the reference field for the GCR simulator.

Slaba et al. (2016)

GCR Simulation Beam consists of 33 beams

- *4 proton energies plus degrader*
- *4 helium energies plus degrader*
- *5 Heavy ions: C, O, Si, Ti, Fe*

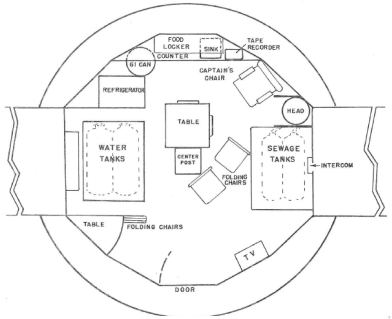
GCRsim beam selection normalized to 500 mGy

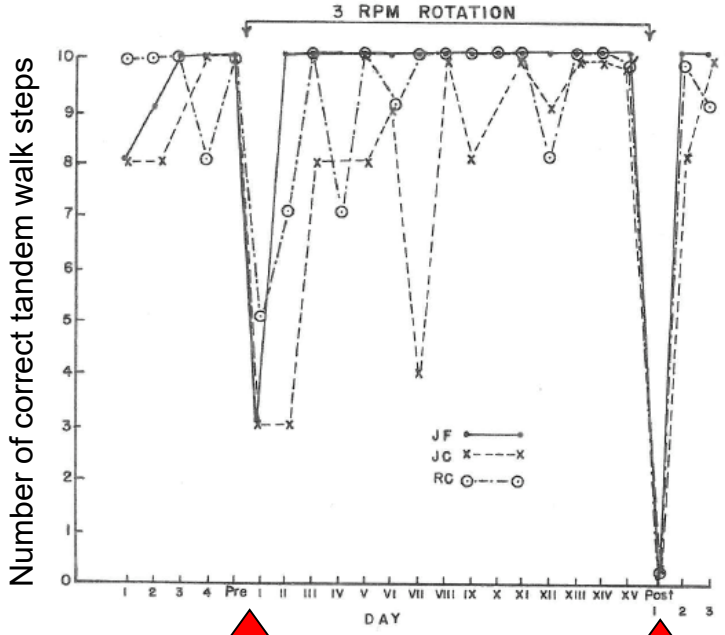
Ion	Energy (MeV/n)	Range (cm)	LET (keV/µm)	Dose (mGy)
^{1}H	20 - 100, 11 steps	*Polyethylene degrader for energies 20 to 100*		
^{1}H	150	15.9	0.54	35.0
^{1}H	250	38.1	0.39	68.9
^{1}H	1000	326.6	0.22	123.6
^{4}He	20 -100, 11 steps	*Polyethylene degrader for energies 20 to 100*		
^{4}He	150	16.0	2.17	7.5
^{4}He	250	38.3	1.56	16.4
^{4}He	1000	327.8	0.88	24.9
^{12}C	1000	110.1	7.95	11.7
^{16}O	350	17.0	20.8	15.4
^{28}Si	600	22.7	50.2	8.1
^{48}Ti	1000	32.5	109.5	4.5
^{56}Fe	600	13.1	175.1	4.1
Total				*500.0*

Centrifugation

Research emphases: research areas and techniques

Slow Rotating Room

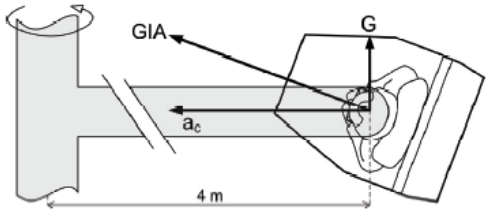


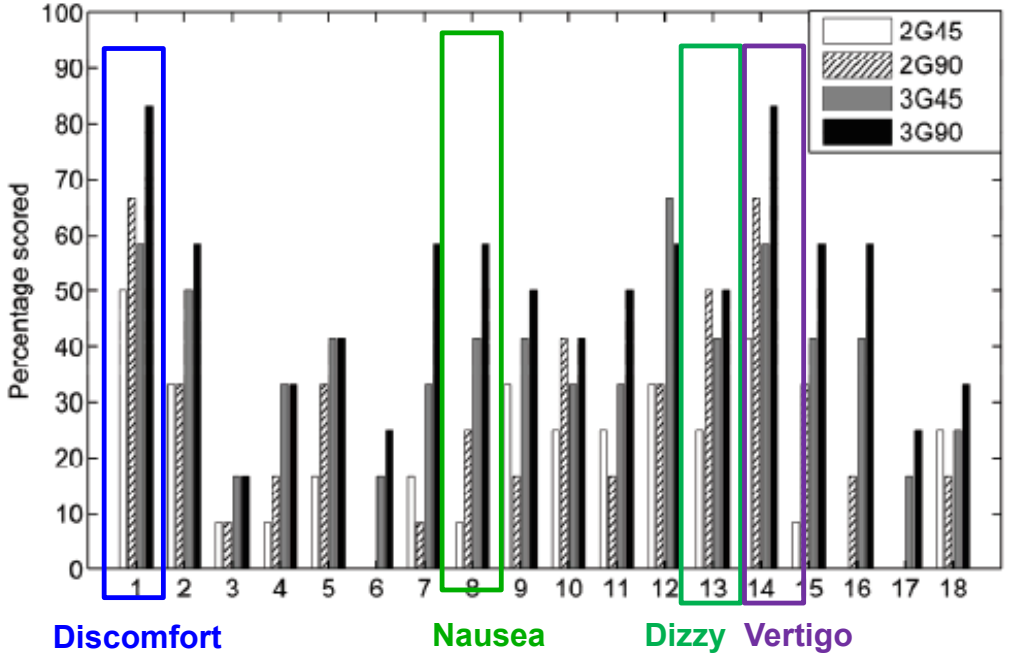


Guedry et. al (1962)

Rotation transition

Gondola Centrifuge





1 = General Discomfort
2 = Fatigue
3 = Headache
4 = Eyestrain
5 = Difficulty Focusing
6 = Increased Salivation
7 = Sweating
8 = Nausea
9 = Difficulty Concentrating
10 = Fullness of head
11 = Blurred Vision
12 = Dizzy (eyes open)
13 = Dizzy (eyes closed)
14 = Vertigo
15 = Stomach Awareness
16 = Burping
17 = Emesis
18 = Oscillopsia

S.A.E. Nooij © Amersfoot, 2008

Bedrest Can be Used to Understand Spaceflight Performance Changes

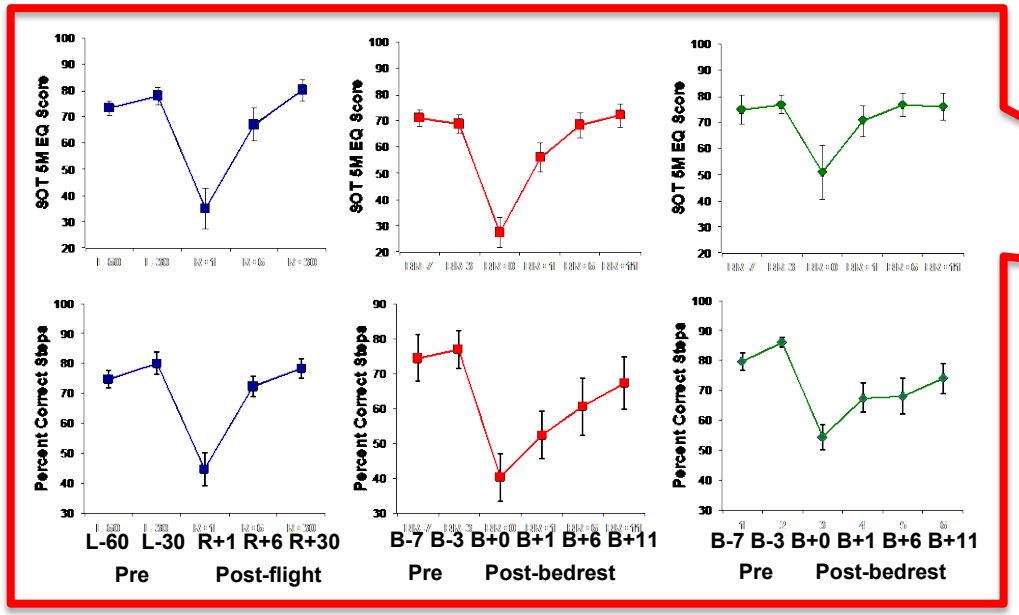
Research emphases: research areas and techniques

Spaceflight modifies:

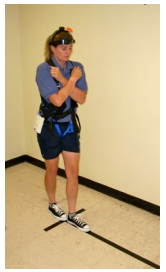
Vestibular **and** body load/proprioceptive information

Bedrest modifies:

Body load/proprioceptive information **without** altering vestibular information



Balance Function



Spaceflight and bed rest subjects showed similar deficits in balance control

Bedrest serves to delineate the role of body unloading /proprioception in spaceflight performance changes

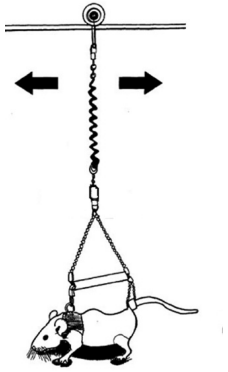
Bloomberg JJ (PI), Functional Task Test Study
Mulavara et al. (2018), Med Sci Sports Exerc

Animal Models

Research emphases: research areas and techniques

Unloading

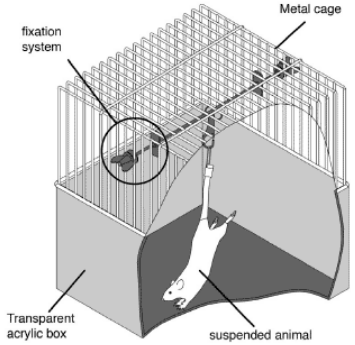
Body-weight Unloading



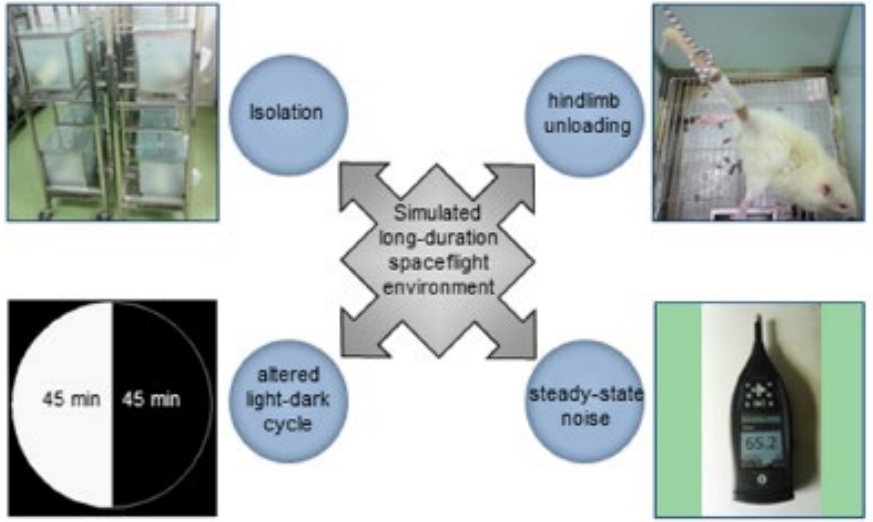
Wagner et al. J Appl Physiol 2010

Hind Limb Unloading

Morey-Holton & Globus, J Appl Physiology 2002



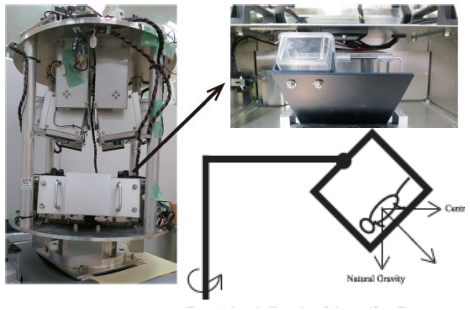
Simulation of combined stressors



Wu X et al. Front. Pharmacol. (2017)

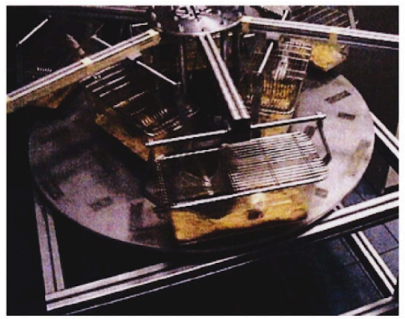
Centrifugation

Centrifuge for Mice



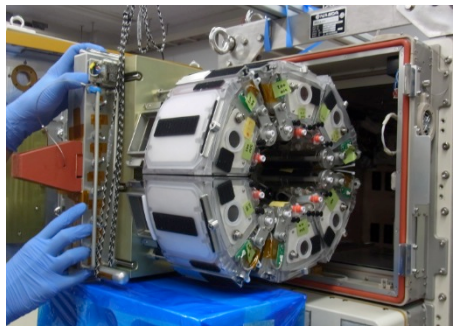
Morita H, et al. (2015) PLoS ONE 10(7)

Turn Table Centrifuge

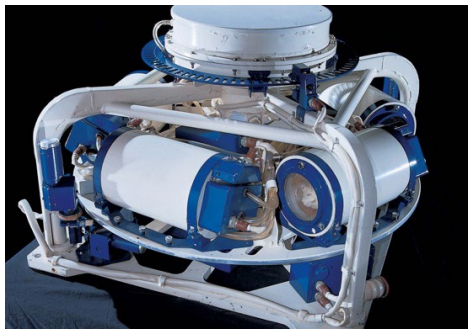


Isolceram (I-00040 Rocca Priora, Italy)

JAXA ISS Mouse Centrifuge



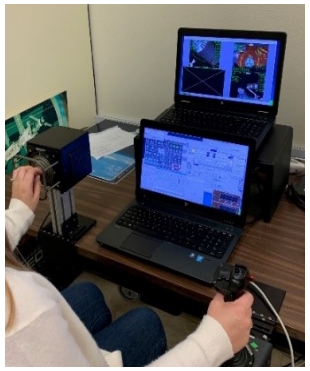
Cosmos-936 Rat Centrifuge



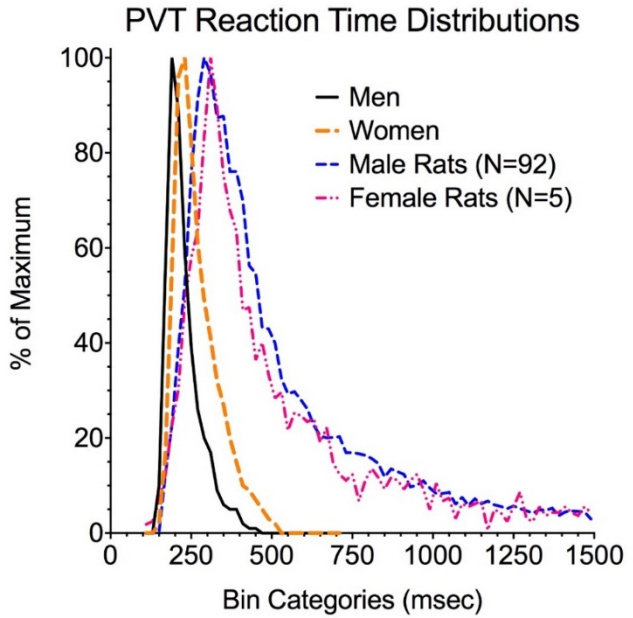
Translations: Animal Research to Human Outcomes

Research emphases: research areas and techniques

Translational models to determine biological effects that lead to brain changes



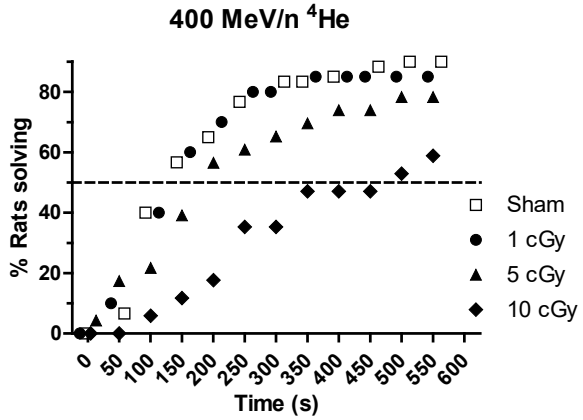
Rodent Reaction Time

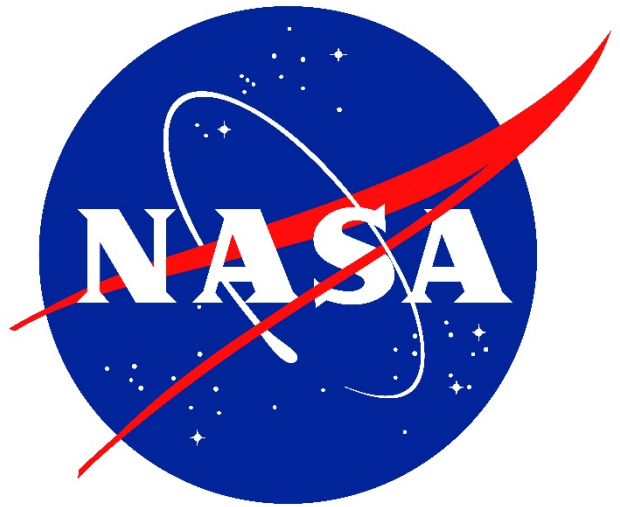


Davis, Roma, & Hienz (2016)

Complex Decision Making

Courtesy of Britten R. (2018)




NASA